02911.000600.

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

OLUWOLE T. ALOBA ET AL.

Application No.: 10/023,748

Filed: December 21, 2001

For: ORAL PHARMACEUTICAL PRODUCTS CONTAINING 17β-ESTRADIOL-3-LOWER ALKANOATE, METHOD OF ADMINISTERING THE SAME AND PROCESS OF PREPARATION

Examiner: San Ming R. Hui

Group Art Unit: 1617

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. §1.132

Sir:

Tina M. deVries, declares and says that:

1. I am the Vice President of Pharmaceutics at Galen Holdings, PLC and have been in this position since November 2000. Prior to this, I was the Senior Director of Research and Development of Pharmaceutics at Warner-Chilcott, which was eventually acquired by Galen Holdings.

2. I graduated from The Ohio State University Graduate School in 1989, with a Doctor of Philosophy in Pharmaceutics and Pharmaceutical Chemistry.

3. I am one of the named inventors of the above-identified United States Patent Application.

4. I am aware that the Examiner has rejected claims 1-3, 5, 10, and 11 under 35 U.S.C. 103(a) as being allegedly unpatentable over U.S. Patent No. 3,478,070 (Stein et al.).

5. I have reviewed the Stein et al. patent and understand it to be a general disclosure for preparing 3-acylated derivatives of d-estradiol. I do not believe that Stein et al. recognized the significant improvement in the relative bioavailability of estradiol found when 17β-estradiol-3-acetate is administered in an oral preparation. In fact, Stein et al. does not even disclose a preparation containing 17β-estradiol-3-acetate.

6. This is exemplified in the specification of the application in Example 3, which details a study comparing the bioavailability of 17β-estradiol-3-acetate to 17β-estradiol. Each participant received (1) one tablet of 1.152 mg 17β-estradiol-3-acetate (equivalent to 1 mg of 17β-estradiol), and (2) one tablet of 1 mg micronized 17β-estradiol (Estrace® Tablets). Treatments were orally administered, with a one-week washout period between treatments.

7. Nine healthy postmenopausal women participated in the study. All participants were Caucasian. The median age was 57 (47-70) years old, with a median weight of 68.5 (55.0-89.0) kg, and a median height of 156 (149-165) cm. Data from eight of the participants was evaluable.

8. Blood samples were collected serially from each participant about 48 hours before and up to 48 hours after receiving the treatment. The blood samples were analyzed for estradiol concentration by a validated GC/MS assay with a lower limit quantitation of 5 pg/mL.

9. Based upon a preliminary evaluation of the data, the improvement in bioavailability of 17β-estradiol-3-acetate over 17β-estradiol was reported to be 15%.

10. Upon a more comprehensive analysis of the data, however, the

improvement in bioavailability was determined to be 19%, rather than 15%. The difference in assessment of bioavailability is attributed to applying a baseline correction to the analytical results. The baseline correction factors into consideration the particular participant's baseline value, i.e., concentration of estradiol in the bloodstream.

11. In my opinion, the result obtained from the comprehensive analysis of the data of Example 3 reflects more accurately, the improvement in bioavailability of the invention, i.e., 17β-estradiol-3-acetate over 17β-estradiol. However, it should be understood that even a 15% improvement in bioavailability over 17β-estradiol would be substantial and unexpected.

12. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Subscribed this 14 day of November, 2003.

Tina deVries, Ph.D

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